Appendix 5: Supportive Clinical Studies

1. Introduction

Studies 403-93-2 and 503-93-2 were multi-center, open-label, single arm, Phase II studies of patients with recurrent or refractory solid tumors of any histology, except Kaposi's sarcoma and HNSCC. The patients had undergone treatment with at least one previous cancer modality, such as systemic chemotherapy, surgery, or radiation, and presented with relapsed or progressive local tumors at study entry. Tumors were treated at a dose of CDDP/epi gel of 0.5 mL/cm^3. The maximum total dose for all tumors treated at one visit was 10 mL. Patients received up to 6 weekly treatments in an 8-week period and were then followed weekly for 4 weeks. Patients who achieved a complete response were followed monthly; patients with partial response or those with recurrence following response or with newly emergent tumors were allowed to receive additional treatments and then followed. During the treatment period, tumors were measured each week using one of the following methods (clinical/physical exam, computed tomography, ultrasound, endoscopy, or colposcopy), and the tumor volume was measured at each visit. Responses were based on reduction in tumor volume using standard definitions of response.

For esophageal cancer patients, a dysphagia assessment was conducted at each visit, and a barium swallow test or esophagoscopy was conducted one week after the patient's last of the six treatments and when clinically indicated during the studies. Because measurement of esophageal tumors was difficult, the protocol permitted change in ability to swallow to be used as an assessment of tumor response in these patients. For patients with obstructing exophytic esophageal cancer, response was assessed based on three specific criteria:

- During endoscopy, the volume of exophytic tumor nodules was estimated using the known width of open biopsy forceps as the reference scale, and response was defined as CR, PR, SD, or PD.
- Dysphagia was graded on a scale of 0 to 4 based on reported ability to swallow different foods. Improvement in dysphagia was defined as one point or greater improvement in the dysphagia grade as assessed by the physician.
- Lumen patency was assessed by radiological or endoscopic examinations of the esophagus. Improvement in lumen patency was defined as at least an one-category increase in size compared to the baseline assessment, sustained for 28 days or more.

Progress toward prospectively selected treatment goals was evaluated using the *Treatment Goals Questionnaire* as it was used in the phase III trials in patients with HNSCC.

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2. Results

2.1. Demographics and Baseline Characteristics

Patient demographics are summarized in Table A6-1. Patients with a variety of recurrent or refractory solid tumors were enrolled in these Phase II studies, without restriction as to the original site of the primary cancer or the histologic type of cancer.

The cancer subgroups differed with respect to gender and ethnicity. All patients with breast cancer were female, 75% of patients with esophageal cancer were male, and all patients with melanoma were white. Of patients with "other" cancers, most (82%) were white.

Table A6-1: Demographics and Patient Characteristics by Cancer Subgroup

Characteristic	Breast (n = 29)	Esophageal (n = 24)	Melanoma (n = 28)	Other (n = 45)	Overall (n = 126)
Age (years)					
N	29	24	28	45	126
Mean (SD)	62 (12.5)	74 (12.0)	61 (12.2)	61 (14.1)	64 (13.7)
Median	63	76	61	63	64
Range	41–87	52–92	39–82	31-88	31–92
Gender					
N	29	24	28	45	126
Male	0 (0%)	18 (75%)	13 (46%)	27 (60%)	58 (46%)
Female	29 (100%)	6 (25%)	15 (54%)	18 (40%)	68 (54%)
Ethnicity					
N	29	24	28	45	126
White	23 (79%)	21 (88%)	28 (100%)	37 (82%)	109 (87%)
Black	1 (3%)	3 (13%)	0 (0%)	5 (11%)	9 (7%)
Asian	1 (3%)	0 (0%)	0 (0%)	1 (2%)	2 (2%)
Other	4 (14%)	0 (0%)	0 (0%)	2 (4%)	6 (5%)
Weight (kg)					
N	28	23	28	44	123
Mean (SD)	67 (19.2)	65 (14.3)	77 (18.2)	70 (17.1)	70 (17.6)
Median	68	66	74	68	69
Range	38–101	44–92	49–121	44-127	38-127
Karnofsky, baseline					
N	28	24	27	45	124
Mean (SD)	85 (14.8)	71 (14.8)	84 (11.2)	83 (14.6)	81 (14.7)
Median	90	70	90	90	90
Range	40–100	40–100	60–100	50–100	40–100

2.1.2. Baseline Disease Characteristics

Typical patients with breast cancer had primary adenocarcinoma with local recurrence or metastases, most often to the chest wall, with associated difficulties of pain, wound management, and limb mobility. Patients with malignant melanoma characteristically had metastases to the chest wall or extremities. Patients with esophageal cancer commonly presented with exophytic tumor growing into and obstructing the esophageal lumen. These patients were treated by endoscopic injection of the exophytic or intramural base of the tumors using small needles, such as those designed for sclerotherapy of esophageal varices. Patients with "other" cancer had a variety of recurrent primary

cancers and superficial metastases that were amenable to injection of CDDP/epi gel by conventional injection techniques, guided by vision and/or physical palpation of the tumor masses. Tumors were chosen for treatment because of local symptomatology. The advanced state of disease in this patient population is illustrated by their extensive prior cancer therapy.

Table A6-2: Previous Cancer Therapy

	n	%
Any Previous Therapy	115	91%
Single Modality	22	18%
Surgery	12	10%
Radiation	5	4%
Chemotherapy	5	4%
Multiple Modalities	93	73%
Surgery and radiation	17	13%
Surgery and chemotherapy	13	10%
Radiation and chemotherapy	10	8%
Surgery, radiation, and chemotherapy	53	42%

2.1.3. Baseline tumor characteristics

All patients enrolled had histologically confirmed**,** recurrent or refractory, primary or metastatic tumors that were accessible for injection with CDDP/epi gel and were measurable. The sites of primary cancer were breast, skin, esophagus, and lung, with remaining primary sites varying widely. The predominant histologic type of the primary cancer was adenocarcinoma, followed by squamous cell carcinoma and melanoma. There were also a variety of other histologies, such as soft tissue sarcomas.

The 126 patients in these studies had a total of 488 individual tumors treated at any time during the trials. For the cancer subgroups, the median tumor volumes for the MTT of patients with breast and melanoma were similar (3.2 and 3.5 cm^3, respectively), whereas the median tumor volumes for the esophageal and "other" categories of cancers were larger (8.4 $cm^3$and 26.2 cm^3, respectively).

Table A6-3: Tumor Characteristics

Cancer Subgroup	Breast	Melanoma	Esophageal	Other
No. of MTT treated	29	28	24	45
Median baseline MTT volume (cm^3) (range)	3.2 (0.4–412.5)	3.5 (0.1–200.6)	8.4 (0.7–124.0)	26.2 (0.5–1400)
No. of individual tumors, total	99	254	35	100
Baseline tumor volume (cm^3) median (range)	0.7 (<0.5–412.5)	<0.5 (<0.5–200.6)	3.0 (<0.5–124.0)	1.8 (<0.5–1400)

2.1.4. Dosing

In the overall study sample, the median dose of CDDP/epi gel per treatment visit was 1.39 mL and the median cumulative dose was 6.15 mL for MTTs of median size 6.5 cm^3. The median fraction of assigned dose administered to the MTT was 59% per treatment visit and 56% cumulatively.

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Table A6-4: Summary of Dosing

	Cancer Subgroup				
Variable	Breast (n=29)	Melanoma (n=28)	Esophageal (n=24)	Other (n=45)	Overall (n=126)
Dose (mL) administered per baseline tumor volume (cm^3)					
Per treatment visit median	0.16	0.29	0.23	0.10	0.16
range	0.013-1.80	0.041-1.05	0.020-0.90	0.002-0.72	0.002-1.80
Cumulative median	0.99	1.33	0.88	0.50	0.92
range	0.075-12.60	0.244-12.00	0.040-4.12	0.012-4.35	0.012-12.60
Dose (mL) administered					
Per treatment visit median	0.90	1.19	1.98	3.00	1.39
range	0.06-5.17	0.05-8.17	0.13-4.20	0.09-10.00	0.05-10.00
Cumulative median	3.60	5.21	5.45	10.00	6.15
range	0.25-31.00	0.25-49.00	0.40-25.20	0.22-190.2	0.22-190.2
No. of treatments median	2	3	3	3	3
range	1-7	1-12	1-6	1-21	1-21

2.2. Primary Endpoints

The primary efficacy variable for the uncontrolled trials 403 and 503 was:

- objective response of the MTT

The association of Patient Benefit with response of the MTT was a key efficacy analysis and is described following the discussions of MTT response and Patient Benefit.

2.2.1. Response of the MTT

Complete or partial response of the MTT of at least 28-day duration occurred in 35% of 124 patients treated with CDDP/epi gel. The response rate was highest in breast cancer (50%) and similar in all other groups (29-33%). The response rate was higher for smaller tumors. For responders, the median time to onset of response was 21 days and the median duration was 85 days (range, 29-637 days).

Of 44 responders to CDDP/epi gel, 35 (80%) continued in local remission at the time of study withdrawal or start of a potentially confounding therapy. Many of these patients who experienced tumor response due to local CDDP/epi gel treatment were not able to extend their participation in the study beyond a few months, due to systemic disease progression, general physical debilitation, or death. The mean time to progression of the MTT for all patients was just over 7 months (214 days, SE 11.0).

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Table A6-5: Response of the MTT

	Breast (n=28)	Esophageal (n=24)	Melanoma (n=27)	Other (n=45)	Total (n=124)
Response Rate (CR+PR)	14 (50%)	7 (29%)	9 (8[d]) (33%)	14 (31%)	44 (43[d]) (35%)
CR	6 (21%)	0	5 (19%)	8 (18%)	19 (15%)
PR	8 (29%)	7 (29%)	4 (15%)	6 (13%)	25 (20%)
Time to Response (days) Mean (SD)	48 (75.1)	12 (6.5)	66 (44.2)	45 (42.3)	45 (53.7)
Median (range)	25 (7–294)	8 (7–21)	62 (13–126)	30 (7–122)	21 (7–294)
Duration of Response (days) Mean (SD)	96 (51.3)	75 (31.9)	163 (213.2)	165 (158.0)	128 (133.3)
Median (range)	82 (29-211)	84 (29-120)	72.5 (30-632)	101 (29-637)	85 (29-637)

2.2.2. Patient Benefit

Attainment of Patient Benefit was based on achievement of prospectively selected Primary Treatment Goals, according to the Treatment Goal Questionnaire and the Patient Benefit Algorithm, as described.

The overall rate of attainment of Patient Benefit for the 124 patients in the uncontrolled studies was 31%. In the esophageal cancer subgroup, investigator-selected Primary Treatment Goals were related to obstruction for all patients: for 22 of 24 patients, the goal was relief of obstruction, and for the remaining two patients, the goal was prevention of obstruction. Likewise in this subgroup, the patient-selected goal for almost all patients was relief of obstructive symptoms (22/24 = 92%); for the remaining two patients, the primary goal was pain relief.

Table A6-6: Percent of Patients who Attained Patient Benefit**)**

Subgroup	n	Benefit Rate (%)
Breast	28	39%
Esophageal	24	21%
Melanoma	27	30%
Other	45	33%
Total	124	31%

2.2.3. Association of Primary Endpoints

Of the 126 patients treated with CDDP/epi gel in Studies 403 and 503, 35% were responders. Of the responders, 52% attained Patient Benefit, and of the nonresponders, 20% attained Patient Benefit. The association between Patient Benefit and response of the MTT was statistically significant ($p < 0.001$).

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For the subgroups of breast cancer and "other" cancers, the association was also statistically significant. In all cancer subgroups, the percentage of patients who attained Patient Benefit was higher in MTT responders than in nonresponders.

Table A6-7: Association of Tumor Response and Patient Benefit

		Responder		Nonresponder		p-value
		n	(%)	n	(%)	
Breast (n=28)	Benefitter	9	64%	2	14%	0.033 [a]
	Non-benefitter	5	36%	12	86%	
Esophageal (n=24)	Benefitter	2	29%	3	18%	0.55 [a]
	Non-benefitter	5	71%	14	82%	
Melanoma (n=27)	Benefitter	3	33%	5	28%	1 [a]
	Non-benefitter	6	67%	13	72%	
Other (n=45)	Benefitter	9	64%	6	19%	0.005 [a]
	Non-benefitter	5	36%	25	81%	
Total (n=124)	Benefitter	23	52%	16	20%	0.0001 [a]
	Non-benefitter	21	48%	64	80%	

[a] Exact Cochran-Mantel-Haenszel test

3. Conclusions of Uncontrolled Studies

Treatment with CDDP/epi gel effectively:

- reduced tumor volume in tumors of various primary origins and in various locations
- achieved tumor responses in patients who had undergone a range of previous cancer therapies and for whom therapeutic options were very limited
- provided patients with symptomatic relief, as measured by the Treatment Goal Questionnaire, indicating that patients received clinical benefit from the treatment.

The association between Patient Benefit and tumor response was statistically significant ($p < 0.001$). In all cancer subgroups, the percentage of patients who attained Patient Benefit was higher in responders than in nonresponders.